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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/955,006 | 09/17/2001 | Robert J. Schneider | 5914-084-999 | 7849 |

20583 7590 09/20/2002

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| EXAMINER | |
|---|---|
| LI, BAO Q | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | 8 |

DATE MAILED: 09/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/955,006 | SCHNEIDER ET AL. | |
| | Examiner | Art Unit | |
| | Bao Qun Li | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *22-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Claims 22-30 are pending.

### *Election/Restrictions*

1. Applicants' election of Group III, claims 15-18 in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a).

2. Since Applicants cancel all claims 1-21 and added new claims 22-30 read on the scope of elected group III, therefore, claims 22-30 are considered before the examiner.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 22-30 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the dosage of the compound, the rout of the administration and the method for modulating and determining the level of cytosolic calcium etc.

Claim 28 is rejected for recitation an unclear short abbreviation BAPTA. Please spell out the full description of BAPTA followed by the short term in the parenthesis when the word is first appear in the claim.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using an in vitro cell line system to demonstrate that the expression of recombinant hepatitis B virus (HBV) X protein (HBx) in cell line increase the activation of Src family tyrosine kinases, wherein the activation of the kinase, such as Pyk2, can be inhibited by

calcium chelator EGTA or calcium channel poison or modulator cyclosporine A (CsA), does not reasonably provide enablement for having an in vivo method for treating patients infected with HBV by using any or all agents, which are able to modulate the cytosolic calcium concentration of a cells in vitro. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to made and use the invention commensurate in scope with these claims.

The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988).

In the instant case, the spate of art teach that function of HBx protein involve the Ras-Raf Map kinase pathway through the activation of the Src family tyrosine kinases summarized by Yen et al. ( J. Biomedical Science 1996, Vol. 3, pp. 20-30). The transfection of HBx protein into HepG2 cells activate. The activation of Src tyrosine kinase increase for HBV DNA replication or mRNA expression. HBx also can activate the proline-rich tyrosine kinase 2 (pyk2), and this activations is blocked by the calcium channel inhibitor CsA or Calcium chelator EGTA, which modulate the cytosolic calcium level as evidenced by Bouchard et al. (Science 2001, Vol. 294, pp. 2376-2378). However, there is no report for using the calcium channel modulator for treatment of HBV reported so far.

Applicants are reminded that the field for treating HBV is very complicated and unpredictable. Although the function of HBx (or Px) is extensively studied for so many years, the true function of HBx protein are still unclear, such as (1) how does Px activates the Ras pathway, and how does this activation affects cellular transcription and cell cycle regulation? (2) is the sole function of Px in nucleus to induce CREB binding to its cognate sites, or does pX also interact with other components of the transcriptional initiation complex.? (3) what is the role of pX in cellular transformation and infection (Yen et al. J. Biomedical Science 1996, Vol. 3, pp. 20-30) because Lee et al. reported that the hepatitis B virus transactivator X protein is not

tumerigenic in transgenic mice (J. Virology 1990, Vol. 64, pp. 5939-5947, see abstract) and Blum et al. disclose that hepatitis B X protein is not central to the viral life cycle in vitro (J. Virol. 1992, Vol. 66, pp. 1223-1227, see abstract). Therefore, the conclusion for targeting the HBx protein is unpredictable.

Applicants are further reminded that treatment with calcium mobilizing inhibitor, such as the claimed cyclosporine A (CsA), which is a systemic immunosuppressant, the side effect of CsA is increase of the susceptibility to infection and the development of neoplasia. ( Please see the Physician Desk Reference http://www.pdrel.com, pages 1)

The present application only teaches that the expression of recombinant HBx protein in the cell lines increase the activation of Src family tyrosine kinase and the signal molecule Pyk2 of Sir kinase activator. The kinase activation is blocked by the treatment of the cell lines with calcium chelator EDTA or calcium channel modulator or poison cyclosporine A (CsA). The treatment of CsA or BAPTA down regulate the expression of HBV DNA or viral mRNA expression as well as the HBV endogenous polymerase activity of HBV pol in the HepG2 cell line in vitro.

The specification presents no working examples of the claimed invention directed to the method for using the calcium modulator for treating HBV infection in an in vivo testing system and in patients.

The specification presents no guidance on how the skilled artisan would practice successfully a calcium modulator, such as EGTA or CsA for treating the patients and address all problems that may happen a patient receiving a systematically use of those agents.

Hence, considering the broad scope of claimed invention, the state of art, the unpredictable of the field it concluded that undue experimentation would be required for a person skill in the art to enable the intended claims.

***Claim Rejections - 35 USC § 103***

Claims 22-30 are deemed free of prior art, given failure of the prior art to teach or reasonably suggest to use a calcium modulator for treating HBV infection. The most closest prior art evidenced by Klein et al. (Molecular and Cellular Biology 1997, Vol. 17, pp. 6427-6436) teach that the HBx protein of hepatitis B virus is a small transcriptional transactivator that

activate the Ras and its downstream Ras signally pathway including Raf, MAP kinase kinase kinase (MEK), and Map kinases. HBx protein stimulates C-Src and Fyn kinases for prolonged time. However, there is no indication for using the calcium modulator for treating the HBV infection.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li
September 18, 2002

ALI R. SALIMI
PRIMARY EXAMINER